

What is claimed is:

1. A method of determining if cancer cells are resistant to an agent, the method comprising:

- 5       determining the p57/KIP2 level in the cancer cells prior to contact with the agent;
- contacting the cancer cells with the agent;
- determining the p57/KIP2 level in the cancer cells after contact with the agent; and
- 10       comparing the p57/KIP2 level in the cancer cells after contact with the agent to the p57/KIP2 level in the cancer cells prior to contact with the agent;
- wherein an increase in the p57/KIP2 level in the cancer cells after contact with the agent compared to the p57/KIP2 level in the cancer cells prior to contact with the agent indicates the cancer cells are resistant to the agent.

15   2. The method of claim 1, wherein the cancer cell is an epithelial carcinoma cell line.

      3. The method of claim 2, wherein the epithelial carcinoma cell lines is selected from the group consisting of an oral squamous carcinoma cell line, a metastatic oral carcinoma cell line, and a breast epithelial carcinoma cell line.

20

      4. The method of claim 1, wherein the cancer cells are derived from a human epithelial carcinoma.

25   5. The method of claim 4, wherein the human epithelial carcinoma is selected from the group consisting of an oral squamous carcinoma, a metastatic oral carcinoma, and a breast epithelial carcinoma.

      6. The method of claim 1, wherein determining the p57/KIP2 level is by detecting the p57/KIP2 protein.

30

      7. The method of claim 1, wherein determining the p57/KIP2 level is by detecting the mRNA encoding p57/KIP2.

8. A method of determining if cancer cells are sensitive to an agent, the method comprising:

- 5 determining the p57/KIP2 level in the cancer cells prior to contact with the agent;
- contacting the cancer cells with the agent;
- determining the p57/KIP2 level in the cancer cells after contact with the agent; and
- 10 comparing the p57/KIP2 level in the cancer cells after contact with the agent to the p57/KIP2 level in the cancer cells prior to contact with the agent;
- wherein no increase in the p57/KIP2 level in the cancer cells after contact with the agent compared to the p57/KIP2 levels in the cancer cells prior to contact with the agent indicates the cancer cells are sensitive to the agent.

15 9. A method of identifying an agent effective for the treatment of a cancer, the method comprising;

- determining the p57/KIP2 level in cancer cells prior to contacting with the agent;
- contacting the cancer cells with the agent;
- 20 determining the p57/KIP2 level in the cancer cells after contacting with the agent; and
- comparing the p57/KIP2 level in the cancer cells after contacting with the agent to the p57/KIP2 level in the cancer cells prior to contacting with the agent;
- 25 wherein no increase in the p57/KIP2 level in the cancer cells after contacting with the agent compared to the p57/KIP2 level in the cancer cells prior to contacting with the agent indicates the agent is effective for the treatment of a cancer.

30 10. A method of determining the therapeutic effectiveness of an agent, the method comprising:

- contacting normal cells with the agent;

determining the p57/KIP2 level in the normal cells after contacting with the agent;

contacting cancer cells with the agent;

determining the p57/KIP2 level in the cancer cells after contacting with the agent; and

comparing the p57/KIP2 level in the normal cells after contacting with the agent to the p57/KIP2 level in the cancer cells after contacting with the agent;

wherein a higher p57/KIP2 level in the normal cells compared to the p57/KIP2 level in the cancer cells indicates the agent is effective for the treatment of cancer.

11. The method of claim 10, wherein the normal cells and cancer cells are cultured together.

12. A method of optimizing the formulation of an agent for the treatment of a cancer, the method comprising:

contacting cancer cells with a first formulation of the agent;

determining the p57/KIP2 level in the cancer cells contacted with the first formulation of the agent;

contacting cancer cells with a second formulation of the agent;

determining the p57/KIP2 level in the cancer cells contacted with the second formulation of the agent; and

comparing the p57/KIP2 level in the cancer cells contacted with the first formulation of the agent to the p57/KIP2 level in the cancer cells contacted with the second formulation of the agent;

wherein the formulation with the lower level of p57/KIP2 indicates the formulation of the agent more effective for the treatment of a cancer.

13. A method of preventing damage to non-cancerous cells in a subject undergoing cancer therapy, the method comprising administering to the subject a polyphenolic composition under conditions effective to induce the expression

of p57, induce the expression of caspase-14, or induce the expression of both p57 and caspase-14 in non-cancerous cells.

14. The method of claim 13 wherein the polyphenolic composition is selected  
5 from the group consisting of green tea polyphenol (GTPP), (-)-epicatechin (EC),  
(-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG) and (-)-  
epigallocatechin-3- gallate (EGCG), and combinations thereof.

15. The method of claim 14 wherein the polyphenolic composition comprises  
10 EGCG.

16. The method of claim 13 wherein the polyphenolic composition is  
administered to the subject prior to, coincident with, or subsequent to the cancer  
therapy.

15

17. The method of claim 13, wherein the cancer is selected from the group  
consisting of oral cancer, esophageal cancer, gastric cancer, colorectal cancer,  
prostate cancer, bladder cancer, skin cancer, and cervical cancer.

20 18. The method of claim 13, wherein the cancer therapy is selected from the  
group consisting of chemotherapy, radiation therapy, and a combination thereof.

19. A method of enhancing the effectiveness of a cancer therapy in a subject  
undergoing cancer therapy, the method comprising administering to the subject  
25 a polyphenolic composition under conditions effective to induce caspase 3-  
dependent apoptosis in cancer cells.

20. A method of preventing damage to salivary glands cells in a subject  
undergoing therapy for oral cancer, the method comprising administering to the  
30 subject a polyphenolic composition under conditions effective to induce the  
expression of p57, induce the expression of caspase-14, or induce the  
expression of both p57 and caspase-14 in the salivary gland cells.

21. A method of treating a skin condition comprising contacting the skin with a polyphenolic composition under conditions effective to induce caspase-14 expression in keratinocytes.
- 5 22. The method of claim 21, wherein the skin condition is selected from the group consisting of psoriasis, aphthous ulcer, actinic keratosis, rosacea, a wound, a burn, a skin condition associated with diabetes, a skin condition associated with aging, and a skin condition associated with altered keratinocyte differentiation.
- 10 23. A method of treating a precancerous oral lesion comprising contacting the precancerous oral lesion with a polyphenolic composition under conditions effective to induce p57 expression in normal epithelial cells and induce caspase 3-dependent apoptosis in precancerous and cancerous epithelial cells.
- 15 24. An *in vitro* method for the identification of an agent that possesses both a cytotoxic effect on tumor cells and a protective effect on normal cells, the method comprising:
- 20 co-culturing normal cells adjacent to tumor cells *in vitro*;  
contacting the co-cultured cells with an agent;  
determining if contact with the agent induces tumor cell death; and  
determining if normal cells survive upon contact with the agent; and  
wherein the induction of tumor cell death by contact with the agent and  
the survival of normal cells upon contact with the agent indicated the agent  
25 possesses both a cytotoxic effect on tumor cells and a protective effect on normal cells.
- 30 25. The method of claim 24, wherein both the tumor cells and normal cells are of epithelial origin.
26. The method of claim 24, wherein both the tumor cells and normal cells are human cells.

27. The method of claim 24, wherein the induction of tumor cell death upon contact with an agent is determined by detecting apoptosis of the tumor cell.
28. The method of claim 27, wherein the tumor cells are a tumor cell line stably transfected with green fluorescent protein (GFP).
29. The method of claim 28, wherein the tumor cell line stably transfected with GFP is the human oral carcinoma cell line OSC-2.
30. The method of claim 24, wherein survival of normal cells upon contact with an agent is determined by detecting the induction of p57 expression in the normal cells.
31. The method of claim 30, wherein the induction of expression of p57 is determined by detecting the p57 protein.
32. The method of claim 30, wherein the induction of expression of p57 is determined by detecting the mRNA encoding the p57 protein.
33. The method of claim 30, wherein the normal cells are normal human primary epidermal keratinocytes or fibroblasts.
34. An agent identified by the method of claim 24.
35. A kit for the identification of an agent that possesses both a cytotoxic effect on tumor cells and a protective effect on normal cells, the kit comprising normal cells, tumor cells transfected with green fluorescent protein (GFP), and printed instructions for the identification of an agent that possesses both a cytotoxic effect on tumor cells and a protective effect on normal cells.